REMARKS

Status of Claims and Claim Amendments

In this Amendment, claims 34 and 52-55 have been amended. Claims 35-37, 40, 47, 51, and 64-65 have been cancelled. Claims 66-74 are new. After entry of this amendment, claims 34, 38-39, 41-46, 48-50, 52-63, and 66-74 will be pending.

Claim 34 has been amended to specify that the influenza VLP comprises influenza HA, NA, and M1 proteins and that the M1 protein is from an avian influenza virus. Support for this amendment can be found throughout the specification, for example, at page 4, line 34 to page 5, line 2, at page 5, lines 9-12, at page 6, lines 3-5, and by Figure 3 and Example 1.

The amendments to claims 52-55 are formalistic in nature and have been made to correct the dependency in light of the amendments to claim 34.

Claims 66 and 67 specify that the HA and/or NA proteins are derived from a mammalian origin. Support for these claims can be found in original claims 6 and 20, as well as in the specification at page 6, lines 13-15.

Claims 68 and 69 specify that the HA and NA proteins are derived from human influenza type A viruses and human influenza type B viruses, respectively. Support for these claims can be found in the specification, for example, at page 6, lines 15-16.

Claim 70 specifies that the HA and NA proteins are derived from H3N2. Support for this claim can be found in the specification, for example, at page 4, third paragraph, and Example 3.

Claims 71 and 72 specify that the HA and/or NA proteins are derived from an avian origin. Support for these claims can be found in original claims 6 and 20, as well as in the specification at page 6, lines 13-15, and Example 1.

Claim 73 specifies that the HA and NA proteins are derived from H9N2. Support for this claim can be found in the specification, for example, at page 4, third paragraph, and Example 1.

Claim 74 specifies that the M1 protein is encoded by the nucleic acid of SEQ ID NO: 3. Support for this claim can be found in the specification, for example, at Figure 3 and Example 1.

Applicants respectfully submit that no new matter has been introduced by way of these amendments.

The Office Action dated January 27, 2009 has been carefully reviewed and the following reply is made in response thereto. In view of the following remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Written Description Rejections under 35 USC § 112

At page 6 of the Office Action dated January 27, 2009, claims 64 and 65 were rejected as failing to comply with the written description requirement. Specifically, the Examiner noted that claims 64 and 65 recite a peptide (the "YKKL" L-domain) and that support for the peptide itself is not found in the specification. Although Applicants do not agree with this rejections, claims 64 and 65 have been cancelled to expedite prosecution. Therefore, withdrawal of this rejection is respectfully requested.

Obviousness Rejections under 35 USC § 103

The Examiner rejected previously pending claims 34-42 and 45-65 under 35 U.S.C. § 103 (a) as obvious over Latham *et al.* (*J. of Virology*, 2001, 75: 6154-6165) ("Latham") in view of Saito *et al.* (*Vaccine*, 2002, 20: 125-133) ("Saito").

The Examiner further rejected claims 43-44 under 35 U.S.C. § 103 (a) as obvious over Latham in view of Saito and Gupta *et al.* (*Vaccine*, 2001, 14: 219-225) ("Gupta").

By way of this amendment, Applicants have amended independent claim 34 to specify that the influenza VLP comprises influenza HA, NA, and M1 proteins and that the M1 protein is from an avian influenza virus.

Applicants respectfully submit that for any one of the following reasons the rejections under 35 USC § 103 should be removed: (1) The Examiner has not established a *prima facie* case of obviousness; (2) The Examiner has not properly considered and evaluated objective evidence of patentability; and (3) The Examiner has improperly applied the test for inherency by suggesting that a claim limitation is probable or possible.

Failure to Establish a *Prima Facie* Case of Obviousness

It is respectfully submitted that there are at least two reasons that the teachings of Latham and Saito do not support a *prima facie* case of obviousness against independent claims 34 or 56, or any of the claims depending therefrom.

(1) *The Combined Teachings of Latham and Saito Do Not Teach or Suggest Each and Every Claim Element*

First, it is respectfully submitted that Latham and Saito do not teach or suggest a VLP comprising an avian influenza virus M1 protein, as recited in independent claim 34 and claims 38-39, 41-46, 48-50, 52-55, and 66-74 depending therefrom, as well as independent claim 56, and claims 57-63, depending therefrom.

To establish a *prima facie* case of obviousness of a claimed invention, all of the claim features must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Since all the limitations of the claims are not taught or suggested by the combination of Latham and Saito, it is submitted that a the *prima facie* obviousness of the claimed invention has not been established.

First, Latham teaches only human influenza proteins and is silent as to creation of VLPs using structural proteins derived from avian influenza strains. Saito teaches the isolation and characterization of the avian influenza strain A/Hong Kong/1073/99 (H9N2). Although Saito thoroughly characterizes the avian strain's HA protein, Saito fails to mention the strain's matrix (M1) protein, much less teach or suggest that the strain's M1 protein would be important to vaccine development. Instead, Saito focuses almost solely on the avian strain's HA protein, stating that "[i]mmunogenicity of the HA protein is a critical issue for vaccine development," and that "[r]eceptor specificity of the HA plays an important role in determining host range of influenza viruses." Saito, page 131, col. 2 to page 132, col. 1. Applicants respectfully submit that one of skill in the art would not have been guided to use the avian M1 protein based upon the teachings of Saito, particularly given that Saito does not teach the avian M1 protein.

As Latham and Saito do not teach or suggest an avian M1 protein (the critical feature of the pending claims), it is respectfully submitted that the teachings of these references do not support a *prima facie* case of obviousness against any of the pending claims. The teachings of Gupta do not cure this deficiency, as Gupta is silent as to influenza proteins or VLPs.

Claim 42 and claims 52-53, depending therefrom, as well as claims 58 and 60, are further allowable over the asserted combination of teachings from Latham and Saito since both Latham and Saito lack any teaching or suggestion of a VLP that "exhibits hemagglutinin or

neuraminidase activity..." Applicants respectfully submit that none of the cited references disclose an influenza VLP, wherein the hemagglutinin (HA) and/or neuraminidase (NA) exhibit activity. Instead, it has been speculated that the HA and NA proteins disclosed by Latham have the claimed activity, stating that:

> "Latham *et al.* and the specification make the VLPs by insect cells and would be expected to have the same properties. The VLPs of Latham *et al.* react with monoclonal antibodies in western blots and on fixed cells and are stated by Latham *et al.* to be useful as vaccines. The VLPs are shown to look like influenza virus particles. The proteins that make the VLP of Latham *et al.* appear to be wild type in structure and antibody binding. The VLPs of the Latham *et al.* would be expected to have the HA and NA activity of influenza." Office Action mailed October 31, 2006, pages 3-4 (emphasis added).

Latham neither shows nor suggests that the disclosed influenza HA and NA components of the VLP exhibit activity (an essential limitation of claims 42, 52-53, 58, and 60). This deficiency is not cured by the teachings of Saito or Gupta, which are both silent with respect to VLPs. Accordingly, it is respectfully submitted that the teachings of these references do not support a *prima facie* case of obviousness against any of claims 34-55, 58, and 60.

No Motivation to Combine

Second, with respect to the subject matter recited of the pending claims, it is respectfully submitted that, without the benefit of hindsight provided by the claims of the above-referenced application, one of ordinary skill in the art would not have been motivated to combine the teachings of Latham and Saito in the manner that has been asserted.

The United States Supreme Court recently reiterated the rule that "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning . . . to support the legal conclusion of obviousness." *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-41, citing *In re Kahn*, 441 F.3d 977, 988 (emphasis added). Although the criteria for finding obviousness was made more flexible by *KSR*, the Court still recognizes an Examiner must establish "an apparent reason to combine . . . known elements." *Id.* To restate, in order to establish a prima facie case of obviousness, the Patent Office has the

burden of establishing a convincing line of reasoning as to why one of ordinary skill in the art would have been motivated to combine teachings from the prior art.

With respect to motivation for one of ordinary skill in the art to combine and modify the teachings of Latham and Saito in the asserted manner, the following blanket assertion, without much support, was made in the Office Action of February 10, 2006: "One of ordinary skill in the art at the time of the invention would have been motivated to make H9N2 VLPs knowing that for influenza pandemic preparedness one of ordinary skill in the art would study new isolates." Office Action of February 10, 2006, page 5. Applicants respectfully submit that while one of skill in the art may have arguably been motivated to incorporate an HA and NA protein from the avian strain H9N2 into a VLP, no support in the art at the relevant time has been provided for motivation to incorporate an avian M1 protein into a VLP.

The prior art provides no teaching, suggestion, or motivation for the use of an avian influenza M1 protein as specified in independent claims 34 and 56 to produce VLPs (Applicants note that both claims specifically require an avian M1 protein). Instead of the teaching a VLP comprising an avian influenza M1 protein, the prior art teaches the use of the human influenza M1 protein to produce VLPs (see the M1 protein of human influenza strain A/Udorn/72 as disclosed by Latham). Specifically, Latham teaches that the human influenza M1 protein "plays a central role in virus assembly and release." *See* Latham, page 6164, column 1. Based upon on the teachings of Latham, Applicants submit that one of ordinary skill in the art would not have been motivated to use an avian influenza M1 protein to produce VLPs. Rather, one of skill in the art would have used the human influenza M1 protein, which was taught by Latham to be important for virus assembly and release.

Furthermore, the skilled artisan would have had no motivation to switch to an avian M1 protein for the production of a VLP because the skilled artisan knows that M1 confers no relevant immunogenicity. With this is mind, it is not surprising that Saito fails to even mention the M1 protein when characterizing the avian strain H9N2, and instead focuses solely on the strain's HA and NA proteins. This is consistent with what was known in the art at the time of filing. Rather than M1, the skilled artisan understood that the influenza proteins HA and NA were the primary antigens leading to the formation of protective immunity against influenza.

This line of reasoning is consistent with statements made by Latham *et al.*, who assert that:

> "This novel approach for the assembly of virus particles has great potential for the design of vaccines against new influenza virus variants. Even extremely dangerous subtype antigen combinations, such as ***H1N1*** (from the 1918 Spanish flu) or an ***HA-NA combination*** with pandemic potential, could be incorporated into VLPs…." Latham, page 6164, col. 1 (emphases added).

As the Applicants have reiterated throughout examination, to create vaccines against new pandemic influenza virus variants, the skilled artisan would have been motivated by Latham to use the human M1 protein from A/Udorn/72 (H3N2) in conjunction with HA-NA combinations from pandemic strains.

The actions taken by VLP scientists following the publication of Latham emphatically support this conclusion. It is telling that researchers more than six years after the publication of Latham and more than four years after Applicant's filing date continued to use the human M1 protein disclosed by Latham for making influenza VLPs, even against non-human, pandemic strains of influenza. For example, Matassov ***et al.*** (Viral Immunology 20(3): 441-452, September 2007) ("Matassov") disclose in 2007 the use of the human M1 protein of Latham in the construction of VLPs designed to protect against the pandemic 1918 Influenza A virus, an H1N1 swine flu variant. As the results section of Matassov indicates:

> "The 1918 VLP vaccine was produced in Sf9 cells after injection with the 1918 baculovirus recombinant (MOI of 1), ***which carries the HA (A/South Carolina/1/1918) and NA (A/Brevig_Mission/1/1918) genes of the 1918 pandemic influenza virus and the M1 and M2 genes derived from influenza A/Udorn/72 (H3N2).***" Matassov, page 446, col. 1.

When mice vaccinated with the 1918 VLPs were challenged, the mice demonstrated significantly lower viral titers in the nose and lungs than did the placebo group. See Matassov, abstract. Therefore, the Matassov paper is clear evidence that skilled artisan was not motivated to deviate away from using Latham's human influenza M1 protein, particularly because the skilled artisan recognizes that M1 confers no relevant immunogenicity. Rather than replacing M1, Matassov understood that replacement of the HA and NA from the human influenza A/Udorn/72 strain with an HA-NA combination from the 1918 pandemic strain was the only replacement necessary for the construction of a VLP conferring protective immunity against the

1918 pandemic strain of influenza. See Matassov, page 442, col. 1, "we present data on the immunogenicity and protective efficacy of a 1918 VLP vaccine *created with the HA and NA genes of the 1918 virus.*" (emphasis added). Accordingly, Applicants submit that based upon the teachings of Latham, one of ordinary skill in the art would not have been motivated to use an avian influenza M1 protein to produce VLPs. Rather, one of skill in the art would have used the human influenza M1 protein, which was taught by Latham to be important for virus assembly and release. The observation that the post-filing literature did in fact use the human M1 protein for the creation of VLPs against pandemic influenza strains is further evidence to support this conclusion.

The deficiencies of Latham are not cured by Saito or Gupta, which provide no teaching or suggestion for using an avian M1 protein for VLP production. While Applicants acknowledge that the Court in *KSR* emphasized the need for a flexible approach to the obviousness question, the Court nonetheless recognized that "a patent composed of several elements is not proved obvious by merely demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. at 1741. Rather, the Court noted, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant filed to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.* (emphasis added).

With the Court's guidance in mind, Applicants respectfully submit that the Examiner has not shown that one of skill in the art would have been prompted to use an avian M1 protein for VLP production as specified by each of the pending claims. There is nothing in the prior art to suggest that replacing the human M1 with the avian M1 would result in a beneficial change. Moreover, researchers making influenza VLPs from pandemic strains more than four years after the Applicant's filing date continued to use the human M1 protein. Accordingly, it is submitted that a *prima facie* case of obviousness has not been established based upon the cited references and therefore the rejections must be withdrawn.

Secondary Considerations of Non-Obviousness

To rebut the purported *prima facie* case of obviousness, Applicants have shown that the VLPs of the present invention have unexpected and surprising properties as compared to the prior art VLPs. Notably, the Applicants' response filed September 12, 2008 included a Declaration by Gale Smith, Ph.D. (the "Smith Declaration") that provided data demonstrating that VLPs comprising avian influenza M1 proteins have advantageous and surprising properties as compared to the prior art VLPs of Latham, which are constructed from human influenza M1 proteins. Specifically, Applicants have shown that a structural feature found in vast majority of avian influenza M1 proteins (a "YKKL" L-domain at amino acid positions 100-103 of M1) is vital to the formation of VLPs and results in the unexpected property of markedly increased VLP formation. *See* Smith Declaration, paragraphs 8-10.

To date, it has not disputed that the results obtained with VLPs comprising an avian M1 protein are surprising. Applicants note that Examiner has acknowledged this fact in co-pending US Application Serial No. 11/372,466, which claims priority from the instant application. During prosecution of US Application Serial No. 11/372,466, the Examiner has stated that "[a]s far as the declaration itself is concerned, it appears that the YKKL motif of avian M1 produces more VLPs than the human seasonal variant..." Office Action mailed January 26, 2009, page 5. Accordingly, Applicants respectfully submit that they have shown the presence of an unexpected and surprising property in the claimed VLPs to support a finding of non-obviousness. As the MPEP at 716.02(a) states, "the presence of a property not possessed by the prior art is evidence of nonobviousness." (emphasis added).

The Office Action Asserts that the Unexpected Results are Insufficient Because the Claimed Invention is Drawn to a Product, Not a Method of Making

Despite Applicants' showing of unexpected results, the Office Action at page 3 indicates that they are insufficient to rebut the *prima facie* case of obviousness. Specifically, it is asserted that the unexpected results are insufficient because the claims are drawn to a product, not a method of making a product:

> "The declaration states in Para#4 'superior for the production of VLPs,' the claims do not require 'production,' they are drawn to a product, not a method. The declaration discusses in Para#3-11 that there is a difference in seasonal human and avian M1 proteins and discusses experiments and mutations used to show the increased production of VLPs. As noted above, the claims are drawn to a product, not a method of making. Applicant has not shown or demonstrated that there is a difference in making the human versus avian influenza VLPs that would show that it was not obvious to succeed in combining Latham *et al.* and Saito *et al.*" Office Action mailed January 27, 2009, page 3.

Applicants agree that the claims are drawn to a product, but dispute the inference that the surprising properties are not applicable to the present claims because the claims are not method claims. As the Examiner has reiterated throughout prosecution, "one of ordinary skill in the art at the time of the invention would have been motivated to **make** H9N2 VLPs knowing that for influenza pandemic preparedness one of ordinary skill in the art would study new isolates," and "it would be *prima facie* obvious to **make** the VLPs of Latham *et al.* with the H9N2 viruses of Saito *et al.* to **make** the claimed avian influenza VLPs..." Office Action of February 10, 2006, page 5 (emphases added).

Applicants respectfully submit that there is an unmistakable and clear nexus between the unexpected properties and the claims in question. Simply stated, the unexpected properties shown by the Applicants are an absolutely critical feature of the claimed product. Specifically, the unexpected property possessed by the VLPs is driven by the avian influenza M1 protein, which is part of the claimed product and a specifically recited limitation in each and every pending claim. See Smith Declaration, paragraph 10. As noted above, the claimed VLPs possess a structural feature (the YKKL L-domain of avian M1) that results in the unexpected property of significantly increasing the level of VLPs obtained from cultured cells. See Smith Declaration, paragraph 11.

In relation to the claimed product, Applicants submit that the ability to assemble correctly and efficiently is a necessary and integral property of a VLP. Applicants respectfully submit that it is improper to suggest that a showing of surprising efficacy for the claimed VLPs is the only evidence Applicants can use to rebut the purported *prima facie* case of obviousness. This proposition is plainly contrary to the MPEP:

> "Evidence that a compound is unexpectedly superior in **one** of a spectrum of common properties . . . can be enough to rebut a prima facie case of obviousness. No set number of examples of superiority is required." MPEP 716.02(a), citing *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). (emphasis added)

Moreover, as stated in the MPEP at 716.02(a),

> "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the **claimed compound** shares with the prior art, can rebut *prima facie* obviousness." (emphasis added).

The ability to assemble at increased levels is a property of the "compound" (VLP) being claimed as conferred by the avian M1 protein. This property is not possessed by the prior art VLPs. As the Smith Declaration describes at paragraph 8b, the VLPs containing the human M1 of Latham are assembled at a level of only 12% compared to VLPs containing the avian M1 proteins of the instant application. Because the Applicants have shown an unexpected property possessed by the claimed compound, it is respectfully submitted that the purported *prima facie* case of obviousness has been rebutted.

The Office Action States that the Applicants have Improperly Attacked References Individually

At page 3 of the Office Action, it is stated that "[a]pplicant and declaration refer to VLPs of Latham *et al.* The rejection is based on two references and the obviousness to combine..." The Office Action further states "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." Office Action mailed January 27, 2009, page 3, citing *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicants submit that they are not attacking references individually. Rather, Applicants have simply compared the claimed invention with the closest prior art cited (Latham). As stated in the MPEP at 716.02(e), when showing unexpected results, the "applicant is **not** required to compare the claimed invention with subject matter that does not exist in the prior art." (emphasis added). Moreover, "requiring applicant to compare [the] claimed invention . . . suggested by the

combination of references relied upon in the rejection . . . 'would be requiring comparison of the results of the invention with the results of the invention.'" MPEP 716.02(e), citing *In re Chapman*, 357 F.2d 418, 422 (CCPA 1966).

As the MPEP specifies at 716.02(e), "evidence of unexpected results must compare the claimed invention with the closest prior art..." (emphasis added). Applicants submit that they have met this burden. Specifically, the Smith Declaration compares the claimed invention with the closest prior art, namely the Latham reference. In doing so, Applicants have shown that only avian influenza virus strains contain the sequence "YKKL" at amino acids 100-103 of the avian influenza M1 protein. See Smith Declaration, paragraph 9. In contrast, human influenza strains, including the human seasonal strain A/Udorn/72 as disclosed by Latham contain a defective "YRKL" L-domain in M1. See Smith Declaration, paragraphs 11-12. The Smith declaration shows a dramatic difference in VLP formation between YKKL containing avian strains such as A/Hong Kong/1073/99 (disclosed in the present application) compared to the YRKL containing human strain of Latham (A/Udorn/72), and provides data demonstrating that the amino acid mutation in the L-domain is essential to the surprising feature. See Smith Declaration, paragraph 8.

In addition, Applicants acknowledge they have the burden of establishing that the results are "unexpected *and* significant." MPEP 716.02(b) (emphasis added). Moreover, Applicants understand "the evidence relied upon should establish 'that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance.' MPEP 716.02(b), citing *Ex Parte Gelles*, 22 USPQ2d 1318 (BPAI 1992) (emphasis added). To this end, Applicants have shown that use of the seasonal human M1 of Latham produces a mere fraction of the VLPs as compared to when avian M1 proteins are used, such as those disclosed in the present application (see Smith Declaration at paragraph 8b, which shows that the YRKL L-domain containing Udorn M1 of Latham yields only 12% of the level of that produced by the YKKL L-domain containing avian M1). Applicants respectfully submit that this difference is clearly statistically significant.

Furthermore, Applicants submit that such a statistically significant unexpected result is also of enormous practical significance. The increased formation and recovery of VLPs with avian M1 is critical to vaccine development. See Smith Declaration, paragraph 12. Using a human seasonal M1 protein such as the one disclosed by Latham does not produce sufficient

quantities of VLPs for use in a vaccine. See Smith Declaration, paragraph 12. As shown by the Smith Declaration, the only way to generate "recoverable amounts of VLPs necessary for vaccine production is through the use of an avian derived M1 protein, such as the one disclosed in the present application" and presently claimed. Smith Declaration, paragraph 12. Accordingly, by showing significant and practical unexpected results compared to the closest prior art, Applicants have done everything required of them to rebut the purported *prima facie* case of obviousness and thus the rejections must be withdrawn.

Improper Obviousness Rejection Based Upon Inherency

Applicants submit that claim 42 and claims 52-53, depending therefrom, as well as claims 58 and 60, are further allowable over the asserted combination of teachings from Latham and Saito since both Latham and Saito lack any teaching or suggestion of a VLP that "exhibits hemagglutinin or neuraminidase activity..." Applicants submit that none of the cited references disclose an influenza VLP, wherein the HA and/or NA exhibit activity. Instead of citing a prior art reference evidencing an influenza VLP possessing HA and/or NA activity, mere speculation has been used to make the obviousness determination:

> "Latham *et al.* and the specification make the VLPs by insect cells and would be expected to have the same properties. The VLPs of Latham *et al.* react with monoclonal antibodies in western blots and on fixed cells and are stated by Latham *et al.* to be useful as vaccines. The VLPs are shown to look like influenza virus particles. The proteins that make the VLP of Latham *et al.* appear to be wild type in structure and antibody binding. The VLPs of the Latham *et al.* would be expected to have the HA and NA activity of influenza." Office Action mailed October 31, 2006, pages 3-4 (emphasis added).

Applicants submit that the Examiner has erred in rejecting claim 42 and claims 52-53, depending therefrom, as well as claims 58 and 60 on the basis of improper inherency. As the court has consistently held, an Examiner cannot establish inherency merely by demonstrating that the limitation is probable or possible. *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981). "Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency."

Scaltech, Inc. v. Retec/Tetra, L.L.C., 178 F.3d 1378, 1384 (Fed. Cir. 1999). "Any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971).

In insisting that there is inherent disclosure of VLPs with HA and NA activity in the art, the Examiner bears an evidentiary burden to establish that the limitation was necessarily present. In this case, no evidence of such activity in the prior art has been provided. Moreover, it cannot be presumed that the HA and NA in the Latham VLPs are active. To express a protein that exhibits activity, the protein must be folded in the correct conformation. Expression and folding is a complex process that may not yield proteins with activity, especially in an *in vivo* system. The references cited above, especially the Latham reference, do not show nor suggest that the disclosed influenza HA or NA components in the VLP exhibit activity. The only evidence the relied upon for the proposition that the Latham VLPs exhibit HA and NA activity has been derived from the Applicants' specification. As noted above, the Office Action of October 31, 2006 states that "Latham *et al.* and the specification make the VLPs by insect cells and would be expected to have the same properties." Office Action mailed October 31, 2006, page 3 (emphasis added). Such reliance to the Applicants' specification is clearly contrary to well established case law. *In re McLaughlin*, 443 F.2d at 1395 ("Any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper.") (emphasis added).

Instead of providing a prior art reference to support the assertion, a post-filing reference by Matassov *et al.* (*Viral Immunology* 20(3): 441-452, September 1, 2007) ("Matassov") has been cited. See Office Action mailed March 12, 2008, page 5. Applicants submit that the reliance on the post-filing reference is improper. As noted above, "...so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971)

(emphasis added). Moreover, as stated in *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993), "a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." Because the suggestion to combine or modify references must occur prior to an applicant's date of invention, an unknown inherency cannot supply this suggestion at the required time. Accordingly, the Matassov reference cannot be used to show the VLPs of Latham inherently possessed HA and NA activity because it was published over four years after the filing date of the present application.

Furthermore, Applicants point out that "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish inherency of that result or characteristic" (emphasis added). If the HA and NA activity limitation is inherently disclosed in the art, it must be necessarily present and a person of ordinary skill in the art would recognize its presence. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999); *Continental Can*, 948 F.2d at 1268-1269 (Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.) Applicants respectfully submit that one of skill in the art at the time of filing would not have known or expected that the VLPs of Latham possessed HA and/or NA activity. It was not until four years after the filing date of the instant application that this property was recognized, and even then, the results were surprising and inconclusive. As stated by Matassov *et al.*:

> "[I]t was important to determine whether the purified 1918 VLPs, which morphologically resemble the influenza virus, were able to agglutinate RBCs. The agglutination assay was performed with RBCs of two different species, chicken and turkey…It was quite surprising to find that the 1918 VLPs were functional in hemagglutination with turkey RBCs, but were unable to perform this function, even at lower dilutions, with chicken RBCs." Matassov, page 446, col. 2.

By relying upon Matassov and the Applicants' specification, the Examiner has erred in concluding the VLPs of Latham inherently possessed HA and/or NA activity. In short, the Examiner has provided no evidence that the Latham VLPs inherently such activity prior to the filing date of the instant application. "With regard to rejections under 35 U.S.C. 103, the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (*i.e.*, the reference teachings establish a *prima facie* case of obviousness) is more

probable than not." MPEP 2142 (emphasis added). In the instant case, the Examiner has not provided any evidence that HA and/or NA in Latham *et al.* has activity. Rather, all that has been provided are assertions that the VLPs of Latham look like influenza particles, antibodies react to these proteins in western blots, and that the proteins appear to be wild type in structure. By using these assertions, the Examiner assumes that the VLPs of Latham "would be expected to have the HA and/or NA activity of influenza."

The mere assertions, however, are not enough. As the Federal Circuit has consistently held, an Examiner cannot establish inherency merely by demonstrating that the asserted limited is probable or possible. *In re Oelrich*, 666 F.2d at 581. Accordingly, Applicants assert that the rejections of claims 42, 52-53, 58, and 60 under 35 U.S.C. § 103 should be withdrawn on the basis of improper inherency.

IV. Conclusions

In view of the foregoing remarks and amendments, it is believed that this application is now in condition for allowance. However, should the Examiner believe that an interview would be helpful to resolve any issues that may remain, the Examiner is invited to telephone the undersigned at the number below.

Please charge the fee for a five-month extension of time to Deposit Account No. 50-1283. Please charge any additional fees deemed necessary and please credit any overpayments to the Deposit Account.

Dated: December 28, 2009

Respectfully submitted,
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